

# Quantitative Genetics

[http://en.wikipedia.org/wiki/Quantitative\\_genetics](http://en.wikipedia.org/wiki/Quantitative_genetics)

## Sir Ronald Aylmer Fisher

<http://www-gap.dcs.st-and.ac.uk/~history/Mathematicians/Fisher.html>

<http://instruct.uwo.ca/zoology/441a/hist3.html>

## Sewall Wright

<http://instruct.uwo.ca/zoology/441a/hist4.html>

<http://www.amphilsoc.org/library/mole/w/wrights.htm>

## J.B.S. Haldane

<http://instruct.uwo.ca/zoology/441a/hist5.html>

## Quantitative variation

Discontinuous traits: Traits that have only a few distinct phenotypes

Continuous traits: Traits that have continuous distributions of phenotypes

### Quantitative vs Mendelian genetics:

#### Biometricians

- most variation in evolution didn't follow Mendelian rules
- continuous / blending variation that varies with environment
- Favors adaptation and survival of the fittest
- Mendelian traits are trivial and not interesting

#### Mendelians

- dismissed biometricians: genotype = phenotype?
- environmentally influenced = not inherited
- evidence supporting Mendelian genetics

Variation **is** continuous and can be inherited...

Continuous variation can be due to:

1. Numerous genes affecting expression (additive)
2. Environmental factors affecting expression (norm of reaction)
3. Both!

**Multiple-factor hypothesis:** many genes produce additive effect.

Polygenes: factors with small, equal effect

Polygenic traits: influenced by genetic variation at many loci

- analysis cannot be done by simple Mendelian genetics
- must compare phenotypic expression in close relatives (known to share a proportion of genes)

### So what's environmental and what's genetic???

First a closer look **norm of reaction**...

## Norm of Reaction

- relationship between environment and phenotype
- many phenotypes from one genotype under different environmental conditions
- phenotypes are constant in an environment (heritability measurements only apply to that environment)

To develop norm of reaction:

1. Develop a homozygous or stable heterozygous line (cloning, selfing)
2. Allow different lines to develop in different environments

Norm of reaction curves

- Plotting the phenotype of one genotype in each environment
- Determines the phenotypic distribution of the trait

## Heritability of quantitative traits

**Heritability**: the proportion of phenotypic variation due to genetic variation

**Heritable** - shared genotype

**Familial** - shared by a family (environmental)

But must account for environmental variation!!!!

**Phenotypic variance** ( $S_p^2$ ) is due to genetic ( $S_g^2$ ) and environmental ( $S_e^2$ ) variance

$$S_p^2 = S_g^2 + S_e^2$$

These variances can also be broken down to include:

- Additive genetic variance (alleles contributing to the genotype)
- Dominance variance (heterozygotes not always an intermediate phenotype)
- Interaction variance (epistatic interactions)
- Environmental variance: general effects, reversible effects and maternal effects
- Covariance between an environment and a genotype
- Genetic-environment interaction

**Heritability**,  $H^2$  is the portion of the overall phenotypic variance due to genetics

$$H^2 = S_g^2 / S_p^2$$

$$H^2 = S_g^2 / (S_g^2 + S_e^2)$$

Non-zero heritability means genetic differences effect trait expression

Perfect heritability (ie: a high  $H^2$ ) does not mean that the environment does not play a part in the variation

### Limits of $H^2$ ...

- Limited prediction of the effect of environmental modification (better with norm of reaction)
- Separation of variance into genetic and environmental components doesn't separate the genetic and environmental causes of variation [<http://www.mun.ca/biology/scarr/fig27-14.htm>]
- high heritability does not mean that a trait is unaffected by its environment.

A trait may have perfect heritability and still change due to environmental variation

Example: IQ scores in adopted children, and their parents

Children	Biological parents	Adoptive parents
110	90	118
112	92	114
114	94	110
116	96	120
118	98	112
120	100	116
Mean = 115	Mean = 95	Mean = 115

### Different Types of Variance That Affect Heritability

Heritability in the broad sense has limits on its usefulness.

We can examine heritability in the narrow sense.

**Additive genetic variance:** due to average differences between carriers of alleles of a QTL.

**Dominance variance:** due to fact heterozygotes are not always exact intermediates between homozygotes.

More than one locus acting on a character->*epistatic interactions*

These interactions will appear as *Interaction variance* ( $s^2_i$ ).

interaction variance is included in dominance variance (nonadditive variance).

Genetic variance is the sum of additive and dominance variance:

$$s^2_g = s^2_a + s^2_d$$

So phenotypic variance:

$$s^2_p = s^2_a + s^2_d + s^2_e$$

More narrow sense of heritability: ratio of additive variance to the phenotypic variance:

$$h^2 = s^2_a / s^2_p$$

Whats the difference?!?

Heritability(*Broad Sense*)  $H^2$ : Phenotypic variance due to genetic variance.

Heritability(*narrow Sense*)  $h^2$ : Phenotypic variance due to **additive variance alone**.

## Estimating Components of Genetic Variance

Hard to estimate all the components of genetic variance.

Easy way to estimate  $h^2$ .

Plot phenotype of offspring vs midparent value.

**Midparent Value**: Average phenotype of both parents.

- Regression line passes through mean of parent and offspring.
- Slope is positive.
- Slope is less than unity.
- Slope represents heritability!!
- Heritability isn't perfect, so neither is slope!

**Selection differential**: Difference between parents and mean of entire population in the same generation.

**Selection response**: Difference between offspring and mean of entire population in the same generation.

$$\text{Selection response} = h^2 \times \text{Selection differential.}$$

If we know other two can rearrange to solve for  $h^2$ !

Done with selective breeding.

$h^2$  will not be same for different populations in different environments.

Environment plays a role that can't be ignored!

## $h^2$ and breeding

$h^2$  used widely in commercial breeding.

Good to make strong lines by selecting for or against traits.

Look for group with a lot of genetic variance for that trait.

*Why?*

- Group with a lot of genetic variance has high  $h^2$
- Higher  $h^2$  = higher parent-offspring correlation!
- Larger fraction of offspring will have wanted trait from parents!

Sometimes forced to work with low  $h^2$ .

When  $h^2$  &  $H^2$  both low:

- Lots of environmental variance!
- **Family selection** used!
- Pairs produce trial offspring, rather than just best individuals.
- Parents selected from progeny that do best.
- Cancels out some of environmental variation.

When  $h^2$  but  $H^2$  high:

- Little environmental variance!
- More dominance variance than additive variance.
- Make use of nonadditive variance.
- **Hybrid-inbred method.**
- Lines made by self crossing.
- These lines are then crossed.
- Choose best hybrid from these crosses.
- Selects for both additive and dominance variance.

Experience with corn makes effectiveness questionable!

## Locating Genes

Its not always possible to locate all the genes that influence a character!

- Only some subsets within a population will be variable.
- Only some variation is actually noticable (i.e Blood group genes).

- Interference from environment can cloud phenotypes.

Genetic analysis only detects a gene if there's variation at that loci.

Molecular analysis can examines DNA and the information it translates!

- We can than look at changes in stretches of DNA, whether phenotype varies or not
- Great for comparing different species!

**candidate gene:** known loci that *may* be responsible for *some* of the phenotypic variance.

## Marker Gene Segregation

**quantitative trait loci (QTL):** Loci whose allelic differences cause variance in a character.

These quatitative trait loci cannot always be identified.

It is possible though to try and track down a region of a chromosome where these QTL's lie.

- cross two lines that differ markedly in QTL's as well as two well known "marker" loci
- If the marker gene is linked to the QTL we can use it to identify the QTL in the next generation.
- Marker genes can be used to "tag" regions of DNA where QTL's lie!

## Linkage Analysis

Marker Gene segregation requires that marker genes are linked to the QTL.

Must be able to make parental lines differing in marker alleles.

Types of molecular polymorphisms used in linkage analysis:

- Restriction fragment length polymorphisms (RFLP's).
- Tandem repeats.
- Single-nucleotide polymorphisms (SNPs).

Such polymorphisms are very abundant.

Makes it likely that two lines will have some differences in known molecular marker loci.

Lines differing in quantitative traits have differences in polymorphisms as well!

### How does Linkage analysis work exactly??

1. Make 2 lines differing in both marker loci and the quantitative trait in loci.

2. Cross the two lines.
3. Cross F1 to itself or backcrossed with parental line.
4. Measure offspring for quantitative phenotype.
5. Characterize genotype and marker loci.

Marker loci & QTL unlinked: All genotypes of the marker show the same average phenotype for the quantitative trait.

Marker loci & QTL are linked: Each marker genotype has different average phenotype.

### Confused?

Think of it this way:

- Marker gene and QTL are unlinked: Independent assortment.
- Marker gene genotype has no bearing on the quantitative phenotype.
- Any marker genotype has the same spread of quantitative phenotypes with same average value.

But...

- If the two are linked then independent assortment doesn't occur!
- Certain alleles of the QTL will separate with certain genotypes of the marker.
- Average phenotype for the A allele is different than that of the a allele!
- Difference depends on strength of the QTL on the phenotype & tightness of the linkage.

If linked we now have a good idea what region the QTL lies in!!

Finding the gene(s) responsible is made much easier, but still a daunting task!!

The gene *may be one of many* influencing the trait, other genes may lie in different regions!

Works great in organisms like *Drosophila*, but human pedigrees are too small to work with!

### LOD Scores

A **LOD score** is a type of statistic. that makes use of a probability ratio.

LOD scores are used to determine linkage distance.

The ratio is the probability of a birth sequence with a linkage of a certain distance divided by the probability of a birth sequence where the genes are unlinked.

The log of this ratio is then taken as a "LOD Score".

Linkage distances with the highest LOD scores are the best estimates of real linkage distances.

Working with logs a LOD score of 2.0 means that it is 100 times more likely.

An example of a LOD Score.

### **Multipoint Mapping**

**Multipoint mapping** is an extension of linkage analysis.

Try to map loci in question against several markers at once!

Lets us know which side of marker loci is on!

LOD score consists of *combined* probabilities!

Makes it hard to compute, use computers!

Using only a few heterozygous loci can take monthes to analyze!!!

### **Othe tools used in quantitative genetics**

#### **Statistics**

Statistical analysis is vital in quantitative genetics.

No clear cut borders for quantitative phenotypes, deal with a range of phenotypes.

For this reason analysis involves measures of central tendency and dispersion

#### **Central Tendancy**

Mean: Average value of a group.

#### **Dispersion**

Variance: How much something differs from the mean value.

#### **Pedigrees**

For comparing phenotypes between offspring we often use pedigrees.

A pedigree is basically a family.

Can be very useful in tracking quantitative phenotypes through multiple generations.

The small size of human pedigrees severly limits the accuracy of linkage analysis.



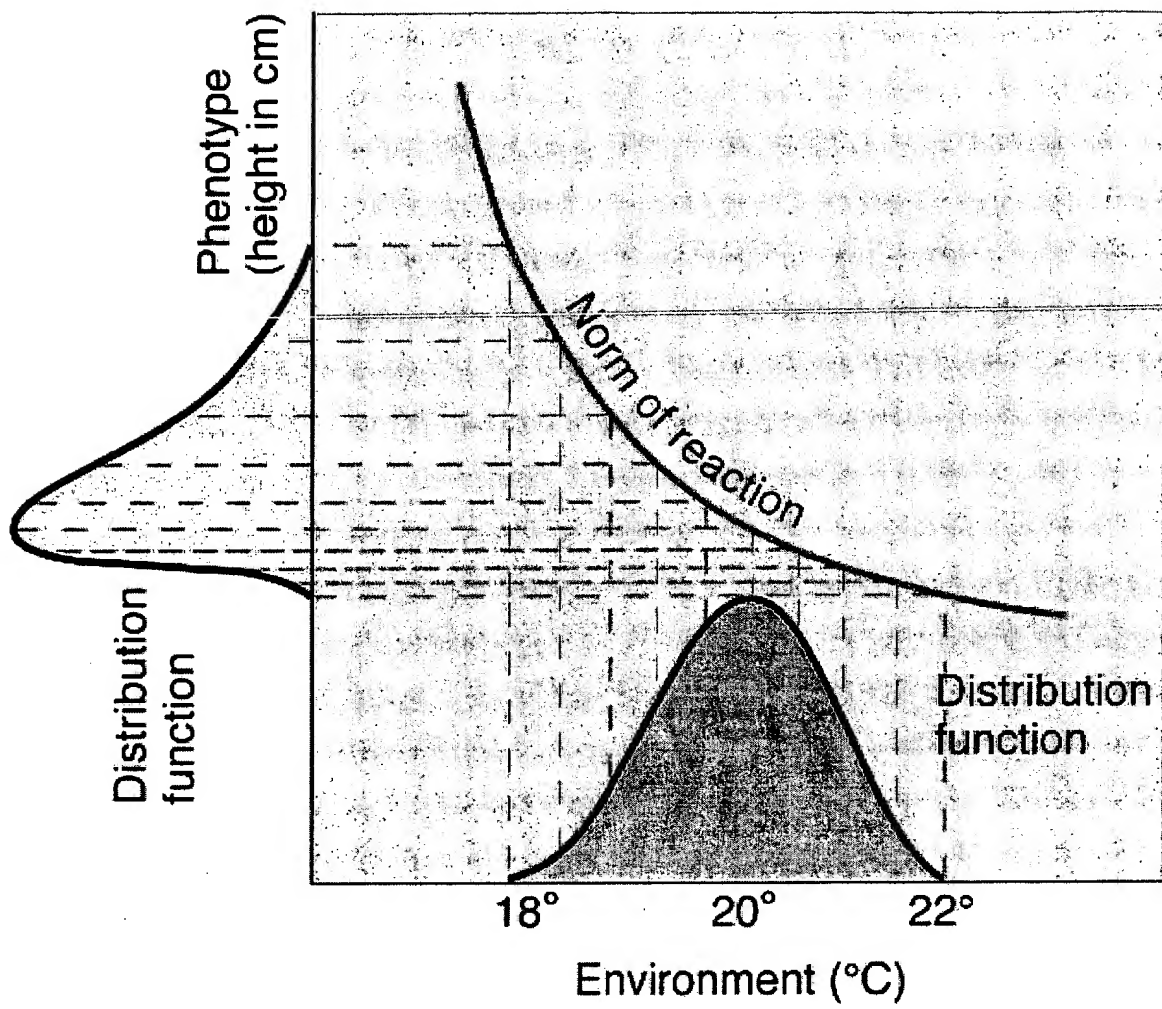
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